

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/26019

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; C07H 21/04

US CL : 435/6; 536/23.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAKANE et al. Effects of Trp ⁶⁴ Arg Mutation in the beta3-Adrenergic Receptor Gene on Weight Loss, Body Fat Distribution, Glycemic Control, and Insulin Resistance in Obese Type 2 Dabetic Patients. Diabetes Care. December 1997, Vol. 20, No. 12, pages 1887-1890, see entire document.	1, 3
A	HANSEN, B.C. Obesity, Diabetes, and Insulin Resistance: Implications from Molecular Biology, Epidemiology, and Experimental Studies in Humans and Animals. Diabetes Care. 1995, Vol. 18, Supplement 2, pages A2-A8.	1-7
A	WILMORE et al. Genetics, Respoinsce to Exercise, and Risk Factors: The HERITAGE Family Study. World Review of Nutrition and Dietetics. 1997, Vol. 81, pages 72-83, especially pages 72-73.	1-7

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

22 February 2000 (22.02.2000)

Date of mailing of the international search report

14 MAR 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Juliet C. Einsmann

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/26019

Continuation of B. FIELDS SEARCHED Item 3: MEDLINE, CAPLUS, WEST (US PATENTS), BIOSIS, EMBASE, SCISEARCH

search terms: diabetes, exercise, allele, polymorphisms, genotype

PCT COOPERATION ...EA

27 2000

PCT

From the INTERNATIONAL BUREAU

To:

GOLDHUSH, Douglas, H.
Nikaido, Marmelstein, Murray &
Oram LLP
Metropolitan Square
655 Fifteenth Street, N.W.
Suite 330 - G Street Lobby
Washington, DC 20005-5701
ETATS-UNIS D'AMERIQUE

**NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES**

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 02 June 2000 (02.06.00)		IMPORTANT NOTICE	
Applicant's or agent's file reference F8172-9031			
International application No. PCT/US99/26019	International filing date (day/month/year) 23 November 1999 (23.11.99)	Priority date (day/month/year) 23 November 1998 (23.11.98)	
Applicant UNIVERSITY OF MARYLAND, COLLEGE PARK et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,JP,KP,KR,MA,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

**AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW**

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
02 June 2000 (02.06.00) under No. WO 00/31297

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

To:
DOUGLAS H. GOLDHUSH
NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP
METROPOLITAN SQUARE, G STREET LOBBY
655 FIFTEENTH STREET, N.W., STE. 330
WASHINGTON, DC 20005 5701

Date of mailing
(day/month/year)

18 JUL 2000

Applicant's or agent's file reference
F8172-9031

IMPORTANT NOTIFICATION

International application No.

PCT/US99/26019

International filing date (day/month/year)

23 NOV 99

Priority date (day/month/year)

23 NOV 98

Applicant
UNIVERSITY OF MARYLAND

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

16 JUNE 2000(16.06.00)

2. That date of receipt is:



the actual date of receipt of the demand by this Authority (Rule 61.1(b)).



the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).



the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.



(If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

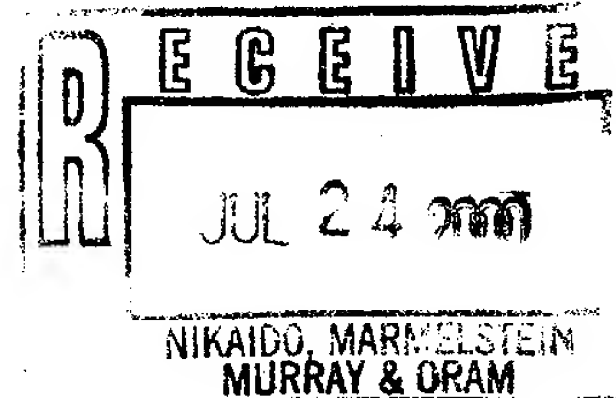
Name and mailing address of the IPEA/
Assistant Commissioner for Patent
Box PCT
Washington, D.C. 20231 Attn:RO/US
Facsimile No. 703-305-3230

Authorized officer

Felicia Lawrence
PCT Operations - IAPD Team 1

Telephone (703) 305-3675 (703) 305-3230 (FAX)

Form PCT/IPEA/402 (July 1998)



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

INVITATION TO CORRECT
DEFECTS IN THE DEMAND

(PCT Rule 60.1)

To:

DOUGLAS H. GOLDHUSH
NIKAIDO, MARMELESTEIN, MURRAY & ORAM LLP
METROPOLITAN SQUARE, G STREET LOBBY
655 FIFTEENTH STREET, N.W., STE. 330
WASHINGTON, DC 20005 5701

Date of mailing
(day month/year)

18 JUL 2000

Applicant's or agent's file reference

F8172-9031

REPLY DUE

within **ONE MONTH** from
the above date of mailing.
See also below.

International application No.

PCT/US99/26019

International filing date
(day month/year)

23 NOV 99

Applicant

UNIVERSITY OF MARYLAND

The applicant is hereby **invited** within the time limit indicated above to **correct the following defects** which this International Preliminary Examining Authority has found in the demand for international preliminary examination:

1. ☐ It does not contain the election of at least one Contracting State bound by Chapter II (Rules 53.2(a)(iv) and 53.7).
2. ☐ It does not permit identification of the international application to which it relates (Rule 60.1(b)).
3. ☐ It does not contain the required petition (Rules 53.2(a)(i) and 53.3).
4. ☒ It does not contain the required indications concerning the agent as specified in the Annex (Rules 53.2(a)(ii) and 53.5).
5. ☐ It does not contain the required indications concerning the international application as specified in the Annex (Rules 53.2(a)(iii) and 53.6).
6. ☐ It is not submitted in the required language which is: _____ (Rule 55.1).
7. ☐ It is not made on the printed form (Rule 53.1(a)).
8. ☐ It is presented as a computer print-out the particulars of which do not comply with the Administrative Instructions (Rule 53.1(a)).
9. ☐ It does not contain the required indications concerning the applicant as specified in the Annex (Rules 53.2(a)(ii) and 53.4).
10. ☐ It does not contain the required signature as specified in the Annex (Rules 53.2(b) and 53.8).

Effect of the date of receipt of the corrections on the date of receipt of the demand:

- (i) If the defects noted under items 1 and 2 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the date when the corrections are received (Rule 60.1(b)). If that date is later than the expiration of 19 months from the priority date, entry into the national phase before the elected Offices will **NOT** be postponed until the expiration of 30 months from the priority date.
- (ii) If the defects noted under items 3 to 10 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the actual filing date (Rule 60.1(b)).

Effect of failure to correct the defects within the time limit indicated above:

- (i) In the case of defects noted under items 1 to 8, this Authority will declare that the demand is considered as if it had not been submitted.
- (ii) In the case of defects noted under items 9 and 10, this Authority will declare that the election(s) of the State(s) concerned is(are) considered as if it(they) had not been made.

A copy of this invitation has been sent to the International Bureau.

Name and mailing address of the IPEA/
Assistant Commissioner for Patent
Box PCT
Washington, D.C. 20231 Attn: RO/US
Facsimile No. 703-305-3230

Authorized officer:

Felicia Lawrence
PCT Operations - IAPD Team 1
(703) 305-3675 (703) 305-3230 (FAX)

Telephone No.

Continuation of item 4: As to indications concerning **the agent** (Rule 4.4), the demand:

- a. ☐ does not properly indicate the agent's name (*specify*):
- b. ☐ does not indicate the agent's address.
- c. ☒ does not properly indicate the agent's address (*specify*):
THE AGENT'S ADDRESS ON THE DEMAND IS DIFFER FROM WHATS ON THE REQUEST.
(PLEASE CLARIFY)

Continuation of item 5: As to indications concerning **the international application**, the demand does not indicate:

- a. ☐ the international filing date.
- b. ☐ the international application number.
- c. ☐ the name of the receiving Office, where the international application number was not known to the applicant at the time the demand was filed.
- d. ☐ the title of the invention.

Continuation of item 9: As to indications concerning **the applicant** (Rules 4.4 and 4.5), the demand:

- a. ☐ does not indicate all the applicants for the elected States.
- b. ☐ does not properly indicate the applicant's name (*specify*):
- c. ☐ does not indicate the applicant's address.
- d. ☐ does not properly indicate the applicant's address (*specify*):
- e. ☐ does not indicate the applicant's nationality.
- f. ☐ does not indicate the applicant's residence.

Continuation of item 10: As to requirements concerning **signature** (Rules 4.15 and 90.4), the demand:

- a. ☐ is not signed.
- b. ☐ is not signed by all the applicants for the elected States.
- c. ☐ is not accompanied by the statement referred to in the check list in Box No. VI of the demand explaining the lack of the signature of an applicant for the election of the United States of America.
- d. ☐ is signed by what appears to be an agent/common representative but
☐ the demand is not accompanied by a power of attorney appointing him.
☐ the power of attorney accompanying the demand is not signed by all the applicants for the elected States.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
RICHARD J. BERMAN
ARENT FOX KINTNER PLOTKIN & KAHN PLLC
1050 CONNECTICUT AVENUE NW
SUITE 600
WASHINGTON DC 20036-5339

PCT

FEB 14 2001

NIKAI DO, MARIELSTEIN
MURRAY & ORAM

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing (day/month/year) 12 FEB 2001	
Applicant's or agent's file reference F8172-9031	REPLY DUE within 1 months/days from the above date of mailing
International application No. PCT/US99/26019	International filing date (day/month/year) 23 November 1999 (23.11.1999)
Priority date (day/month/year) 23 November 1998 (23.11.1998)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6; 536/23.5	
Applicant UNIVERSITY OF MARYLAND	

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 23 March 2001 (23.03.2001).

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer

Juliet C. Einsmann

Telephone No. (703) 308-0196

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

I. Basis of the opinion

1. With regard to the **elements** of the international application: *

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-13, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the claims:
 pages 14-15, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the drawings:
 pages none, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>2, 4-7</u>	YES
	Claims <u>1 and 3</u>	NO
Inventive Step (IS)	Claims <u>2, 4-7</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-7</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by Sakane *et al.*

Sakane *et al.* teach a method for improving diabetes status in a subject in need of such improvement, said method comprising identifying a subject with diabetes having a "11" genotype (where "11" is homozygous for not having the mutation) (Table 1) for the beta-3 adrenergic receptor gene and engaging the subject in extensive exercise for a period of time sufficient to improve the diabetes status in the subject (Table 2). Sakane *et al.* found that subjects with the mutation had smaller decreases in body weight and had difficulties in improving glycemic control and insulin resistance (p. 1889).

Claims 2, 4, 5, 6, and 7 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an association between these particular alleles and an improved diabetes status following exercise.

Claims 1-7 meet the criteria set out in PCT Article 33(4) for industrial applicability.

----- NEW CITATIONS -----
NONE

WRITTEN OPINION

International Application No.

PCT/US99/26019

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 2-7 do not clearly or appropriately define what the "11" and/or "12" genotypes actually represent.

WRITTEN OPINION

International Application No.
PCT/US 2019

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

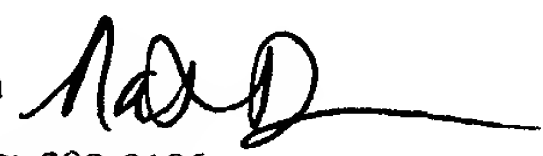
PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

21 JUN 2001

Applicant's or agent's file reference F8172-9031		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/26019	International filing date (day/month/year) 23 November 1999 (23.11.1999)	Priority date (day/month/year) 23 November 1998 (23.11.1998)	
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; C07H 21/04 and US Cl.: 435/6; 536/23.5			
Applicant UNIVERSITY OF MARYLAND, COLLEGE PARK			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>4</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 16 June 2000 (16.06.2000)		Date of completion of this report 23 May 2001 (23.05.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Juliet C. Einsmann  Telephone No. (703) 308-0196	

Form PCT/IPEA/409 (cover sheet)(July 1998)

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-13 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the claims:
pages 14-15, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/26019

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims 2, 4-7

YES

Claims 1 and 3

NO

Inventive Step (IS)

Claims 2, 4-7

YES

Claims 1 and 3

NO

Industrial Applicability (IA)

Claims 1-7

YES

Claims NONE

NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1 and 3 lack novelty under PCT Article 33(2) as being anticipated by Sakane *et al.*

Sakane *et al.* teach a method for improving diabetes status in a subject in need of such improvement, said method comprising identifying a subject with diabetes having a "11" genotype (where "11" is homozygous for not having the mutation) (Table 1) for the beta-3 adrenergic receptor gene and engaging the subject in extensive exercise for a period of time sufficient to improve the diabetes status in the subject (Table 2). Sakane *et al.* found that subjects with the mutation had smaller decreases in body weight and had difficulties in improving glycemic control and insulin resistance (p. 1889).

Claims 2, 4, 5, 6, and 7 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an association between these particular alleles and an improved diabetes status following exercise.

Claims 1-7 meet the criteria set out in PCT-Article 33(4) for industrial applicability.

-----NEW CITATIONS-----

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/26019

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 2-7 do not clearly or appropriately define what the "11" and/or "12" genotypes actually represent.